Remarks

Claims 39-63 are pending. Claims 53-61 have been amended. Claims 39-52, 62, and 63 have been withdrawn from consideration. Claims 70-72 have been added. The specification has been amended to include requisite SEQ ID NOs and appropriate capitalization and generic terminology of trademarks. The sequence listing is also amended to include disclosed but unidentified sequences. The claims have been amended to make them clearer. Specifically, Claim 53 is amended to make it clearer, with support in the claim as originally filed. Claims 55 and 58 are currently amended to depend from Claims 54 and 57, respectively. Support for the amendments to the specification and claims are described below. Thus, no new matter is added by these amendments, and their entry is respectfully requested.

Specification

A. The Office notes the inclusion of oligonucleotide sequences in the specification that are not accompanied with the requisite SEQ ID NO. The specification is currently amended to correct these omissions.

The Sequence Listing is also amended to include the sequences disclosed but not identified. Support is found in the specification as filed where these sequences appear. The paper copy and computer readable form of the paper copy are the same and include no new matter.

B. The Office notes the use of trademarks NONIDET P-40 and TWEEN 20 in the application without the appropriate capitalization and generic terminology. The specification is currently amended to respect the proprietary nature of the trademarks and to include the generic terminology. No new matter is added.

C. The Office objects to the paragraph "Incorporated by Reference" as omnibus language that fails to specify what specific information the applicants seek to incorporate by reference and similarly fails to teach with detailed particularity just where that specific information is to be found in each of the cited documents. Applicants acknowledge this objection to the specification. However, it is not clear that the Office is requiring applicants to amend the specification, or what the legal basis for such a requirement might be. Therefore, applicants have not taken specific action in this regard.

D. The Office notes two claims numbered 43 in the instant application. The claims starting with the second claim 43 were renumbered by the Office as claims 44-69, but the Office notes that the dependencies of the claims were not renumbered. The claims are currently amended to contain correct dependency to the renumbered claims. No new matter is added.

Information Disclosure Statement

The Office notes the listing of specific references listed in the specification that were not included in the information disclosure statement filed August 1, 2002. The Office states that unless the references have been cited by the examiner on form PTO-892, they have not been

considered. In recognition of the requirement that for references to be considered they must be cited in a separate Information Disclosure Statement (IDS), the applicants submit herewith a supplemental IDS.

Claim Rejections – 35 USC § 112, second paragraph

A. Claims 53-61 are rejected as allegedly indefinite in that the full name of the abbreviations TTP, ARE, TZF, TTP-like, TNF-α, GM-CSF are not used in the first occurrences of the abbreviations in the claims. Claims 53, 56, and 59 are currently amended to include the full name for these abbreviations.

B. Claims 54-61 are rejected as allegedly indefinite in that they depend from a non-elected claim (claim 52). Claims 54-61 are currently amended to depend from elected claim 53.

Claim Rejections – 35 USC § 112, first paragraph

A. Claims 53-61 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office cites *University of Rochester v. G.D. Searle & Co.* 68 USPQ2D 1424 (WDNY 2003) at 1428, which states that "the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing." In the cited decision, the plaintiffs had a claim to a method of using a composition, i.e., a COX-2 inhibitor, based on a screening method for discovering said composition. This screening method was based on the discovery that only the inducible COX-2, and not the ubiquitous COX-

1, was relevant to inflammatory disease. The court noted that the compositions that will perform the claimed method were not actually disclosed, nor was there any evidence that such a composition was known at the time of filing. Based on this, the court decided that the inventor had failed to sufficiently describe the method of using the compound such that one of ordinary skill in the art would recognize that they actually possessed the method of using the compound at the time of filing.

The Office is inappropriately applying this court decision, as the facts of the *Rochester* case are not consistent with the present facts. Unlike the *Rochester* case, the applicants are not claiming a method of using a compound. Rather, the applicants are claiming a method of identifying, i.e., screening for, a compound based on the clearly described interaction between a TTP zinc finger domain and an AU-rich element (ARE). In fact, it was determined by the United States Court Of Appeals For The Federal Circuit that the *Rochester* specification did in fact comply with the written description requirement for claims to assay methods, stating that "[t]he only claims that appear to be supported by the specification are claims to assay methods, but those claims were already issued in the '479 patent." *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 928 (Fed. Cir. 2004). Thus, the reasoning in Rochester, when properly applied to the present facts, supports a finding that the present screening method claims satisfy the written description requirement of 35 U.S.C. 112, first paragraph. The present claims are directed to a screening method based on the discovery that TTP contributes to the mRNA degredation of GM-CSF and TNFα via the binding of a zinc finger domain in TTP to an AU-rich element in GM-CSF and TNFα. Thus, the instant method comprises screening for an agent that modulates the disclosed binding of TTP and TTP-like polypeptides with AREs. The applicants

disclose in the specification on page 30-31 cell-based and cell-free assays for determining whether a compound interferes with TTP (or related protein) binding to AREs or with mRNA stability. The applicants direct the Office to page 30, line 8, wherein the applicants disclose the following:

> A variety of assay methods can be used to determine whether a given compound interferes with TTP or related protein binding to the GM-CSF ARE and the breakdown of GM-CSF mRNA. These would include cell-based experiments, such as the transfection studies in 293 cells cited in Example 3; it can be seen that addition of cell-permeable compounds to the cells that inhibited the TTP-mRNA interaction would result in inhibition of TTP's ability to deadenylate and destroy the mRNA. Such assays could use a variety of more convenient readouts, e.g. luminescent proteins, human growth hormone, chloramphenicol acetyltransferase, beta-galactosidase, etc. Similar cell based studies could also be performed in yeast, where there is considerable precedent for high-throughput screening assays for protein interactions with DNA, RNA and other proteins. Cell-free assays would probably be the most convenient to set up; these would involve extracts from cells expressing TTP or its related proteins (e.g., ERF1, ERF2, etc.) or its active fragments (e.g., the double zinc finger domain), and testing their ability to bind to purified, labeled GM-CSF ARE, assayed by either crosslinking or gel-shift assays as described in the Examples. More conveniently still, these assays could use purified TTP or its active fragments, or purifed members of the TTP-related protein class or their active fragments, or fusion proteins expressing TTP or its related proteins or their fragments. All have been shown to be active at binding and crosslinking to the TNFα ARE. These would use variable lengths of sequence of the ~~GM-CSF~~ GM-CSF ARE – e.g., a probe that corresponds to bases 3390 – 3467 of Genbank accession number X03020, but the experiments with the TNF ARE have shown that this could probably be shortened to a "core" ARE of about 23 bases (bases 1309 to 1332 of Genbank Accession number X02611and corresponding bases for GM-CSF).

Thus, the steps of the method of screening for an agent that modulates an activity of TTP are described. The applicants further disclose in the specification (page 31, line 13 to page 32, line 8) examples of compounds that can be screened using the provided screening method. The description of the screening method steps and the underlying relationships are sufficient evidence of possession of a screening method claim. It is not required that the specification provide

exemplification of a compound being screened by the provided method in order to fully describe the screening method. Should the Office disagree, applicants respectfully request that the Office disclose the legal basis for this requirement.

The Office also asserts that "none of the examples is drawn to the claimed method." This statement fails to acknowledge the exemplification of the method steps in the examples. For example, the applicants use a cell-free assay to demonstrate the ability of human TTP to bind the ARE of TNFα-3'-UTR in Example 2 (page 55, lines 7 to 20), wherein the applicants disclose the following:

> To test whether TTP affected binding of cellular proteins to this region of the TNFα mRNA, we transfected 293 cells with a construct expressing epitope-tagged human TTP (21), and attempted to cross-link proteins in a cytosolic extract from these cells to a 153 bp probe from the mouse TNFα 3'-UTR (25) that spanned the ARE. In untransfected cells, the radiolabeled mRNA probe was cross-linked to a major protein species of ~85 kDa. When extracts from TTP-expressing cells were used in a similar experiment, labeling of the 85 kDa protein decreased while a new binding protein of ~40 kDa appeared.
>
> Immunoprecipitation with an antibody specific to the epitope tag revealed that the 40 kDa protein was TTP itself. Expression of the tagged protein in these cytosolic extracts was confirmed by Western blotting; the protein that reacted with the epitope tag antibody also reacted with TTP antibodies. Essentially identical results were obtained when the probe was a 70 bp fragment consisting only of the TNFα ARE (25).

The applicants further exemplify (page 76, lines 4-23) the use of electromobility shift assays to determine the binding of TTP to TNFα ARE. Also exemplified (Example 3, page 70, line1-25) is a cell-based system for determining the ability of a vector encoding a TTP to modulate mRNA (TNFα) accumulation:

> Both TTP and TNFα mRNAs were readily detected when the cells were transfected with either TTP or TNFα expression plasmids. There was a complex relationship found between the concentration of transfected CMV.hTTP.tag DNA and the resulting TNFα mRNA accumulation in the absence of actinomycin D

> treatment. At low concentrations of transfected DNA (5 and 10 ng per plate), TNFα mRNA accumulation was ~ 20% of control, as determined by scanning densitometry of the Northern blot. This decrease in mRNA amount was accompanied by the appearance of a smaller species of mRNA, which first became apparent at 5-10 ng of DNA, but was more obvious at 50 ng. As described below, we believe this lower band to be the deadenylated form of the TNFα mRNA. Beginning at 50 ng DNA through all higher concentrations used essentially *all* TNFα mRNA was in this smaller form. However, the total *amount* of TNFα mRNA accumulation *increased* substantially at higher concentrations of DNA (see below) to reach a maximum of 214% of control at 500 ng. It remained high at 1 μg before decreasing to 51% of control at 5 μg. A similar but "right-shifted" dose-response relationship was present with the genomic TTP construct H6E.HGH3', which uses the weaker native TTP promoter rather than the CMV promoter; in this case, 2 μg of DNA decreased total TNFα mRNA accumulation to 16% of control (n = 3); higher concentrations (5 and 10 μg) resulted in continued expression of the smaller species in greater amounts.
>
> The predominance of the smaller band and the almost complete absence of the larger band could be seen more readily after actinomycin D exposure, presumably because the larger band represented recently synthesized TNFα mRNA that was more likely to be full-length. In this case, 5 and 10 ng of CMV.hTTP.tag DNA resulted in less than 10% of control TNFα mRNA expression.

As provided above, the applicants have explicitly disclosed routine technology in the context of the steps of the present method. The applicants describe the ARE sequence (above) sufficient to create a nucleic acid probe. The applicants further provide the minimum 64 amino acid TZF consensus sequence for TTP or TTP-related proteins that can be used in the above disclosed assays (page 18, line 5-10; pages 10-11). The technology required to practice binding assays using the provided sequences, including for example the addition of epitope tags to the TTP polypeptide, are well known in the art and considered routine. The applicants further provide a general description of agents that can be used in the provided method (page 31), and specific examples of agents that are expected to compete for TTP binding to ARE without TTP-like activities (page 22). The applicants further provide the use of an inhibitor of transcription such as actinomycin D (above) to prevent compensation by upregulated gene expression, i.e. an

exemplification of claim 60. Thus, the steps of the claimed methods are exemplified. The only step not exemplified is the step of contacting the assay system with a putative inhibitor.

However, it is not required that the specification provide exemplification of the screening method in order to fully describe the method. For a screening method claim based on the present disclosure of the underlying mechanism, it is sufficient to describe the steps of said method. In this regard, the steps of the claimed methods are explicitly described in the specification at the places noted above. In fact, most of the steps are also exemplified as noted above. The only step not exemplified is the step of contacting the assay system with a putative inhibitor. Thus, applicants need not and do not rely on what is described in the art or in the cited documents for description of the claimed method. The applicants therefore request that this rejection be withdrawn.

B. Claims 53-61 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. This rejection is based on the above alleged argument that none of the examples are directed to the claimed methods and that the cited documents are not properly incorporated by reference. The Office is arguing that the applicants' claim is not enabled due a requirement for undue experimentation. The provided method is directed to identifying a compound based on the described interaction between a TTP zinc finger domain and an ARE. The claim is to a method for identifying the compound, i.e. a screening method, not a claim to a composition that would require undue experimentation to identify. Methods for evaluating binding between TTP and ARE are clearly described and exemplified in the

specification (see above). It is therefore unclear what undue experimentation the Office believes would be involved in practicing the claimed screening method.

The Office states that the specification fails to teach the essential method steps, starting materials, and the reaction conditions required to practice the full scope of the invention. As shown above, there is adequate teaching of the provided method based on the discovery of the critical interaction between TTPs and AREs, the required sequences to create the starting materials (e.g. probes), the instruction to use routine methods of evaluating protein mRNA binding, and the exemplification of these methods (see above). Given this teaching, there is no factual basis to dispute the enablement of the present screening method claims. The applicants respectfully request that this rejection be withdrawn.

No payment is believed due, however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

Gwendolyn D. Spratt
Registration No. 36,016

NEEDLE & ROSENBERG, P.C.
Customer Number 36339
(678) 420-9300
(678) 420-9301 (fax)

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I hereby certify that this correspondence and any items indicated as attached or included are being deposited with the United States Postal Service as Express Mail Label No. EL970612199US in an envelope addressed to: [Mail Stop: Amendments (if included in address)], Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Scott Darnell — Date: March 28, 2005